Lifestyle Alterations Pathway Example

Sunday, November 9, 2008

Lifestyle Pathway:

Diet (and exercise) intervention to reduce breast cancer risk

Stephen Barnes, co-chair

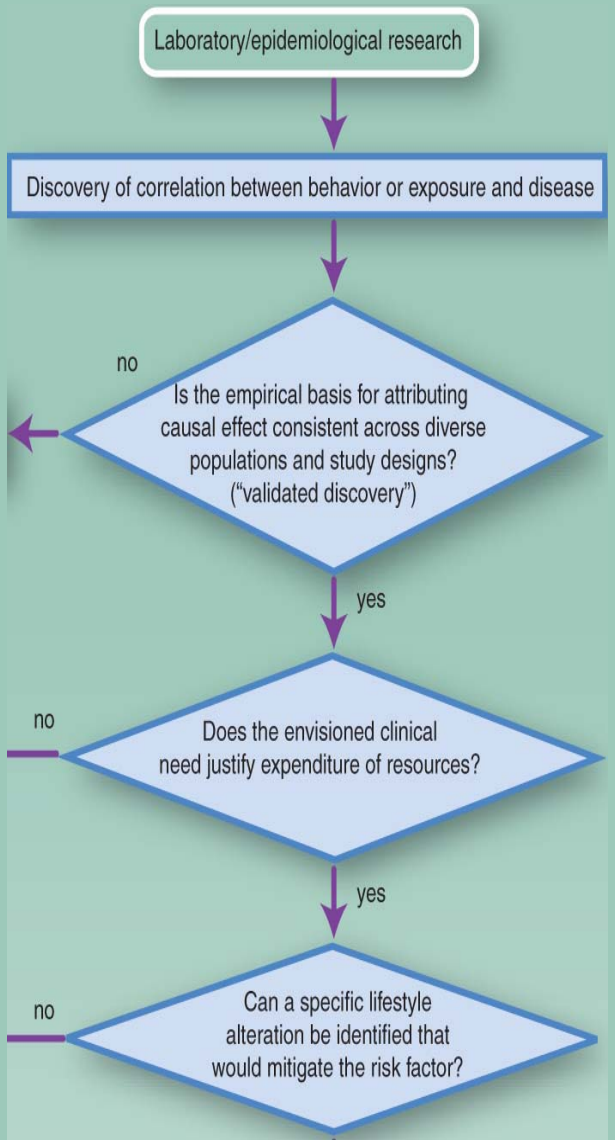
Henry Thompson, Susan Lutgendorf, Deborah Bruner

Ardeth Obenauf, Joyce Graff, Patricia Goldman, Valerie Guild

Abstracts:

177. Barnes et al. Puberty and polyphenol-containing diets and breast cancer risk
183. Dashwood. Dietary histone deacetylase inhibitors for cancer prevention…
185. Kristal et al. Biomarkers for caloric restriction……
187. Meskini et al. Fatty acid synthetase for ovarian cancer.
194. Thompson et al. Coupling dieting for weight loss and chemoprevention…
195. Young et al. Discovery and validation of molecular targets, biomarkers…..
196. Yu et al. Mammary progenitor cells as targets…….

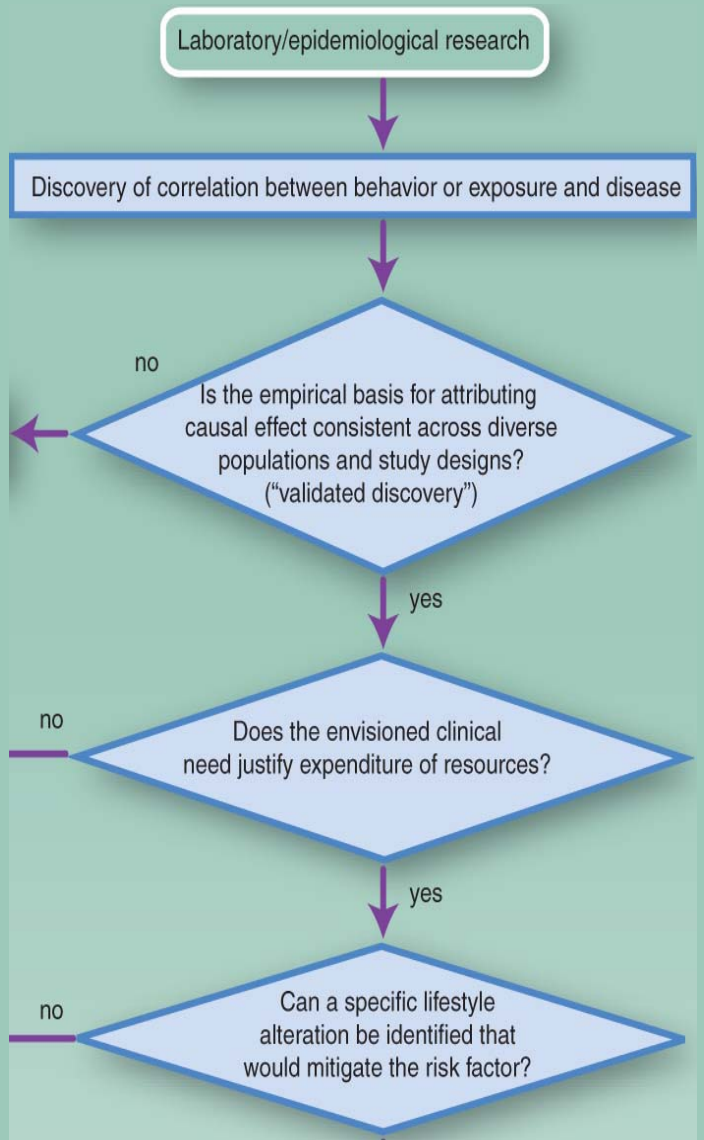
Lifestyle Pathway:
Credentialing: Scientific validation



- Epidemiologic studies of world populations have revealed that there is a large inter-country difference in breast cancer (BC) risk
  - Low risk BC immigrant groups arriving in the USA in adult life maintain a lower risk of BC
  - There is a shift to high risk BC in the second generation of low immigrant groups to the USA
  - These data suggest that dietary exposure and/or exercise in early life and its impact on gene expression are important factors in BC risk
  - Replicated in animal studies (see later)

Shimizu H. et al. Br J Cancer 1991;63:963-6.
Katanoda K. et al. Jpn J Clin Oncol 2007;37:638–639.
Stemmermann GN. Breast Cancer Res Treat. 1991;18:S67–72.

Lifestyle Pathway:
Credentialing: Clinical need



- Since BC mortality is second only to lung cancer in the USA, a reduction of BC by diet and exercise would have an enormous social and economic impact
- Diet and exercise is critical in many ways other than just for cancer, so support for diet and exercise changes may receive broad NIH support
- The goal for nutrition in childhood should be a shift to quality rather than amounts of foods
  - Avoid establishing the sweet tooth!
  - Avoiding obesity at square 1

Lifestyle Pathway:
Creation of Modality

Specify lifestyle alteration

- Diet and exercise, even in early life, is a critical determinant of gene expression, thereby establishing lifetime risk and BC prevention in adults
- Dietary and exercise habits of children set the scene for their health throughout their entire life
  - Partnership between NCI, NIH, and other agencies and the Food Industry is a critical event in implementing a research strategy
  - Other agencies include **Susan Komen Foundation**
- Observation rather than intervention trials; e.g., identification of female athletes and non-athlete sisters (by-standers) — will assess exercise and diet

Lifestyle Pathway:
Supporting tools:

Identify target population via existing databases or new studies

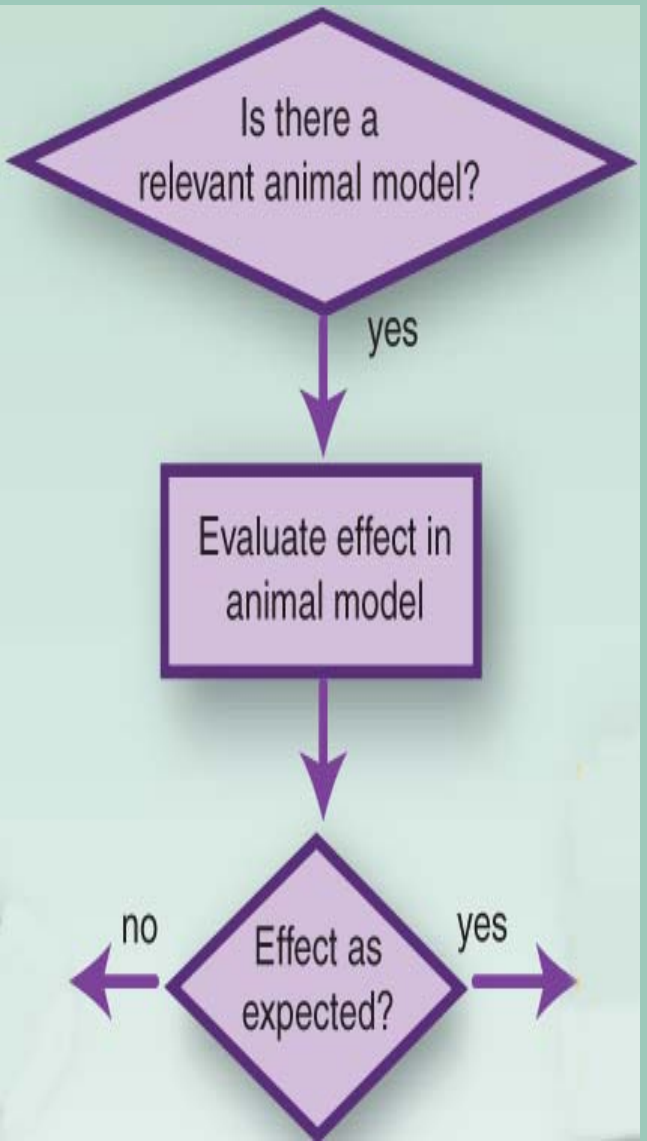
- For breast cancer we need a population of girls who are being followed as they go through puberty
  - In a previous observational study, we have collected blood, urine, buccal swabs, diet histories and information about pubertal changes over a 2 year period in girls from Asian and Caucasian backgrounds who had estimated soy isoflavone intakes of <3 mg/day and >12 mg/day (177)
- A study whereby the girls are studied for a longer period is essential to identify the parameters associated with increased BC risk
  - NIH has just announced the National Children's Study where 100,000 children will be followed from birth to age 21 — a $3.2 Bn investment
  - **Susan Komen Foundation has a biospecimen repository of breast tissue from healthy, normal women of all ages**

Lifestyle Pathway:
Supporting tools:

Develop and validate biochemical, behavioral and/or imaging "assays" to measure effect of lifestyle alteration*

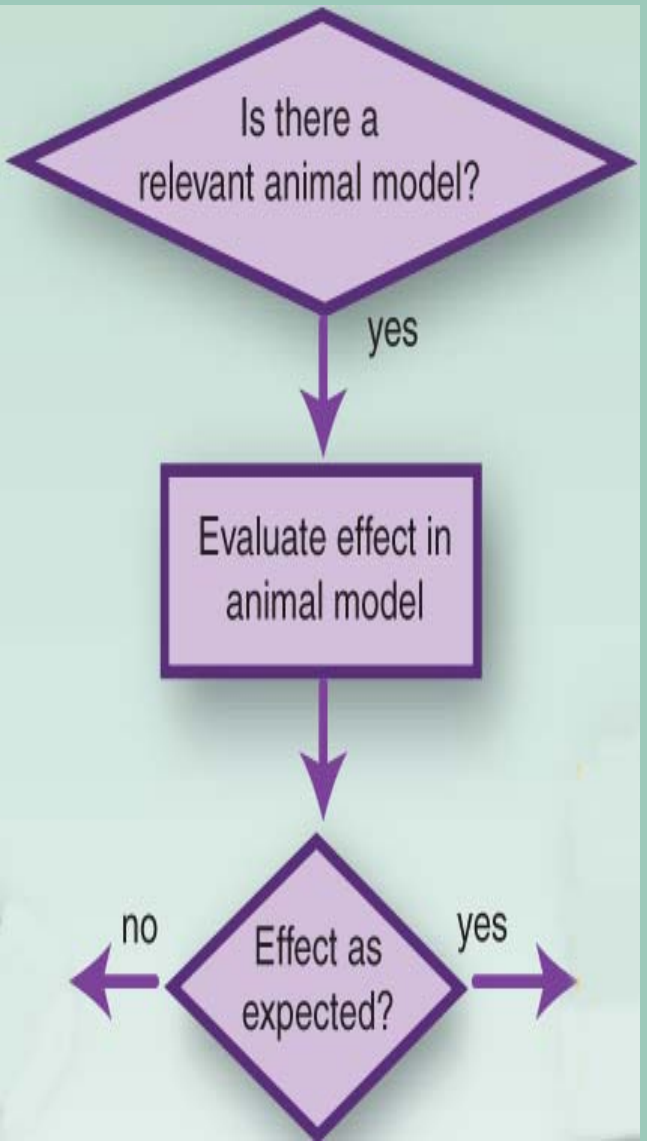
- Early childhood and the onset of puberty is accompanied by many factors
  - Puberty in girls starts with gradual increases in steroid hormones, thereby leading to increased expression of specific genes and appearance of proteins
  - Further development in puberty leads to a marked period of tissue rearrangement and increased bone deposition
- Study of the peptidome in the urine will reflect these changes and can be used to identify the critical stages in early childhood and pubertal development
  - New R21 study funded by NCCAM to do this (177)
- Study of histone acetylation status in human white cells in girls undergoing interventions involving diet, exercise and pharmacological approaches on mitochondrial function
  - Approaches taken by Emily Ho and Rod Dagwood (183)
  - Top down proteomics using FT-ICR MS
- Metabolomics in blood and urine to establish changes in intermediate metabolism (Bruce Kristal — 185)

Lifestyle Pathway:
Preclinical Development



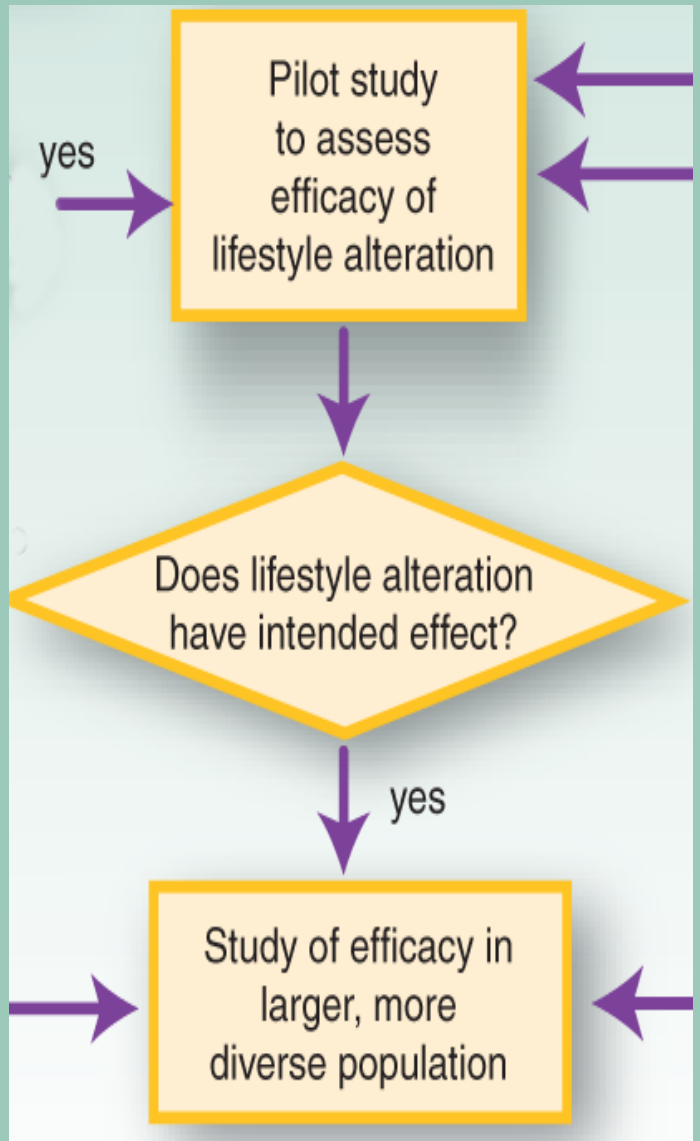
- Chemically-induced mammary tumor rodent models
  - These have shown that several dietary phytochemicals are chemopreventive (177)
  - Genistein's action is age-dependent and is not effective in adults (177)
  - Age-dependence of other phytochemicals to be determined

Lifestyle Pathway:
Preclinical Development



- Effect of diet/exercise intervention on specific-cancer related targets
  - Mouse models with targeted gene disruption
    - Wei Yu et al. Targets of mammary gland stem cells (196)
  - Gene knockdown of specific proteins/enzymes identified from microarray and proteomics experiments (yeast phenotype high throughput screens)
  - *In vivo* protein turnover imaging
- Targets identified as candidates for assessing onset of cancer phenotype:
  - HIF-1α
  - Fatty acid synthase (an inhibitor of this enzyme has been developed) (187)
  - mTOR

Lifestyle Pathway:
Clinical Trials



- Retrospective and observational trials have been performed
  - Retrospective dietary records from observational studies have shown that tofu consumption in adolescence is associated with lowered BC risk (XO Shu, Shanghai Cancer Registry)
  - Prospective observational trial in low and high soy consumers to determine whether soy influences onset of puberty has just finished (Horn-Ross, NCCC)
- New areas for clinical trials
  - Exercise-based intervention with participants in “Run for the Cure” events promoted by the Susan Komen Foundation
  - US girls soccer is the best in the world — opportunities for observational trials